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(21) International Application Number: PCT/US00/09472 (22) International Filing Date: 6 April 2000 (06.04.00) (30) Priority Data: 60/127,984 6 April 1999 (06.04.99) US (71) Applicant: PHARMAQUEST LTD. [—/—]; Reid House, 31 Church Street, Hamilton HM 12 (BM). (71)(72) Applicants and Inventors: MIDHA, Kamal, K. [CA/—]; 195 South Shore Road, Paget, Hamilton (BM). TEICHER, Martin [US/US]; 40 Livingstone Lane, Waltham, MA 02453 (US). (74) Agents: REED, Dianne, E. et al.; Reed & Associates, 3282 Alpine Road, Portola Valley, CA 94028 (US).		(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: PHARMACEUTICAL DOSAGE FORM FOR PULSATILE DELIVERY OF <i>d-threo</i> -METHYLPHENIDATE AND A SECOND CNS STIMULANT (57) Abstract <p>Novel pharmaceutical dosage forms provide for pulsatile delivery of <i>d-threo</i>-methylphenidate and a second CNS stimulant, i.e., release encapsulated drug in spaced apart "pulses". The second CNS stimulant may be an analeptic agent or a psychostimulant, with analeptic agents preferred. The dosage forms may comprise capsules housing compressed tablets or drug-containing beads or particles, or may comprise a tablet with the first, second and optionally third dosage units each representing an integral and discrete segment thereof. Methods of treatment using the pharmaceutical dosage forms are provided as well.</p>		

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PHARMACEUTICAL DOSAGE FORM FOR PULSATILE DELIVERY
OF *d-threo*-METHYLPHENIDATE AND A SECOND CNS STIMULANT

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Patent Application Serial No. 60/127,984, filed April 6, 1999.

TECHNICAL FIELD

The present invention relates generally to drug delivery, and more specifically relates to novel pharmaceutical dosage forms that provide pulsatile delivery of *d-threo*-methylphenidate in combination with a second CNS stimulant. The invention additionally relates to methods for administering methylphenidate using the novel dosage forms.

BACKGROUND ART

Pharmaceutical dosage forms are known which provide a variety of drug release profiles, including immediate release, sustained release, and delayed release. That is, it may be desirable, for a particular drug, to prevent drug release after drug administration until a certain amount of time has passed (so-called "timed release"), to provide substantially continuous release over a predetermined time period (so-called "sustained release") or to provide release immediately following drug administration (i.e., "immediate release"). For some types of drugs, it is preferred to release the drug in "pulses," wherein a single dosage form provides for an initial dose of drug followed by a release-free interval, after which a second dose of drug is released, followed by one or more additional release-free intervals and drug release "pulses." Pulsatile drug delivery is useful, for example, with active agents that have short half-lives and must be administered two or three times daily, with active agents that are extensively metabolized presystemically, and with active agents which lose the desired therapeutic effect when constant blood levels are maintained. These types of agents have pharmacokinetic-pharmacodynamic relationships that are best described by a clockwise "hysteresis loop." A drug dosage form that provides a pulsatile drug release profile is also

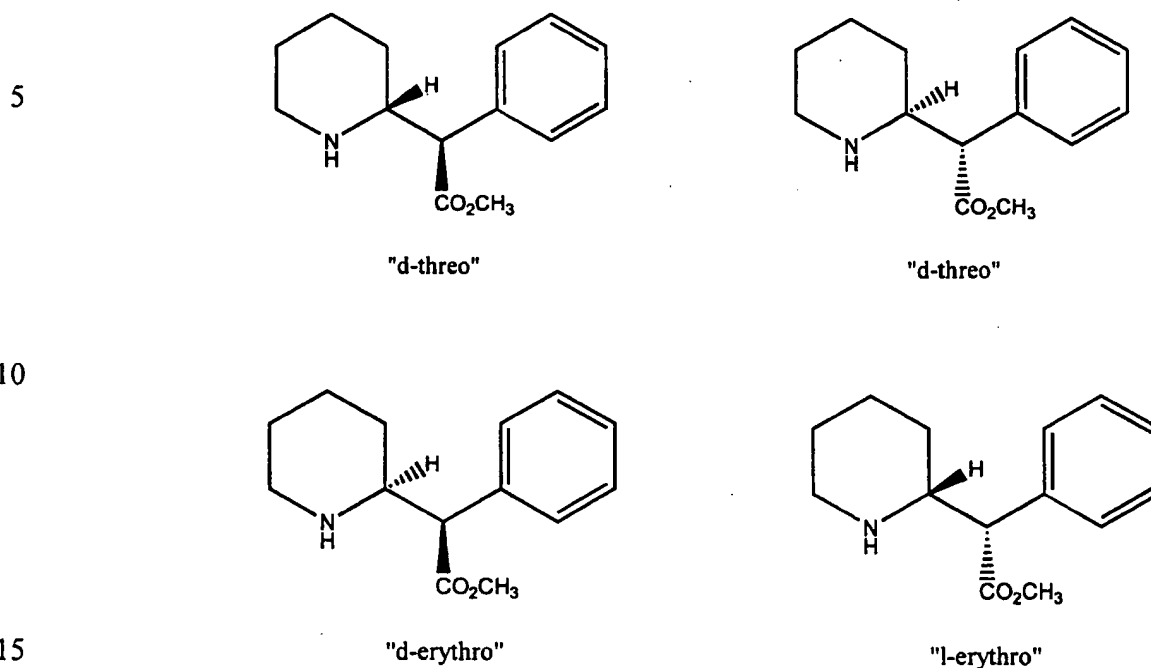
useful for minimizing the abuse potential of certain types of drugs, i.e., drugs for which tolerance, addiction and deliberate overdose can be problematic.

Because a precise and effective pulsatile drug delivery system is difficult to formulate and manufacture, there are few such dosage forms that have been commercialized. There are, however, several patents and literature references pertaining to pulsatile drug delivery. See, for example, U.S. Patent No. 5,413,777 to Sheth et al., directed to a pulsatile once-a-day delivery system for the administration of minocycline; U.S. Patent No. 5,260,068 to Chen, directed to a multiparticulate pulsatile drug delivery system; U.S. Patent No. 4,777,049 to Magruder et al., directed to an osmotic delivery system for constant release of a drug with intermittent release "pulses"; U.S. Patent No. 5,391,381 to Wong et al., directed to a drug dispenser for delivering individual drug-containing units in a "pulsatile" manner; PCT Publication No. WO 98/32424, pertaining to pulsatile delivery of diltiazem hydrochloride; U.S. Patent Nos. 5,472,708 and 5,260,069 to Chen; Ishino et al. (1992) "Design and Preparation of Pulsatile Release Tablet as a New Oral Drug Delivery System," *Chem. Pharm. Bull.* 40(11):3036-3041; Cohen et al. (1994), "Pulsatile Release from Microencapsulated Liposomes," *J. Liposome Res.* 349-360; and Gazzaniga et al. (1994), "Chronotopic Drug Delivery Systems for Pulsatile and/or Site-Specific Release," *21st. Proc. Int. Symp. Controlled Release Bioact. Mater.*, pp. 744-745.

The present invention is directed in part to a novel pulsatile drug delivery system which is straightforward to manufacture and provides precisely timed drug release "pulses" at desired intervals.

Methylphenidate hydrochloride (HCl), the hydrochloride salt of α -phenyl-2-piperidine-acetic acid methyl ester (available commercially as Ritalin[®]), is a central nervous system stimulant that is used in the treatment of Attention Deficit Disorder ("ADD"), a commonly diagnosed nervous system illness in children that is characterized by both distractability and impulsivity. Methylphenidate HCl is also used to treat a related disorder, Attention Deficit Hyperactivity Disorder ("ADHD"), in which symptoms of hyperactivity are present along with the symptoms of ADD. The drug is additionally used in the symptomatic treatment of narcolepsy, depression, and the cognitive decline associated with Acquired Immunodeficiency Syndrome ("AIDS") or AIDS-related conditions, as well as for mood

elevation, particularly in terminally ill patients with diseases such as cancer. Methylphenidate exists as four distinct isomers, as follows:



The drug as used in therapy is a racemic mixture of the *d*- and *l*-*threo* enantiomers, which have been acknowledged as more active than the erythro pair.

Because of its potential for tolerance (loss of clinical efficacy when constant blood levels are maintained), short-half life and potential for abuse, methylphenidate is a primary candidate for use in conjunction with the drug delivery systems of the invention.

It has recently been found that the *d*-*threo* enantiomer of methylphenidate, rather than the *l*-*threo* enantiomer, is primarily responsible for the therapeutic effectiveness of methylphenidate, particularly in ADHD. See Srinivas et al. (1992), "Enantioselective Pharmacokinetics and Pharmacodynamics of *d,l*-*threo*-Methylphenidate in Children with Attention Deficit Hyperactivity Disorder," *Clin. Pharmacol. Ther.* 52:561-568, who compared the results of administering *dl*-*threo*, *d*-*threo*, and *l*-*threo* methylphenidate to children suffering from ADHD, and determined that the pharmacodynamic activity of methylphenidate resides in the *d*-*threo* isomer. Ding et al. (1997), "Chiral Drugs: Comparison of the Pharmacokinetics of [¹¹C]*d*-*threo* and *l*-*threo*-Methylphenidate in the Human and Baboon Brain," *Psychopharmacology* 131:71-78, and Eckerman et al. (1991),

“Enantioselective Behavioral Effects of *threo* Methylphenidate in Rats,” *Pharmacology Biochemistry & Behavior* 40:875-880, also studied the relative therapeutic efficacy of the *d-threo* and *l-threo* isomers, concluding that *d-threo*-methylphenidate was responsible for the therapeutic efficacy of the racemate.

5 It has also been suggested that *l-threo* methylphenidate not only makes no contribution to therapeutic efficacy, but in fact contributes to undesirable side effects associated with administration of racemic methylphenidate, e.g., insomnia, euphoria, development of tolerance to the drug, and potential for abuse. Accordingly, several researchers have proposed administering methylphenidate as the pure *d-threo* isomer rather
10 than as the racemic mixture of *d-threo* and *l-threo* isomers. See, e.g., U.S. Patent No. 5,908,850 to Zeitlin et al., U.S. Patent No. 5,874,090 to Baker et al., and U.S. Patent No. 5,922,736 to Dariani et al. Also see U.S. Patent No. 5,837,284 to Mehta et al., which describes a pulsatile drug delivery system for administration of *d-threo* methylphenidate.

A drawback of the prior art, however, is that the disclosed dosage forms are
15 ineffective for individuals who do not respond, or respond inadequately, to methylphenidate therapy or to a second central nervous system (“CNS”) stimulant (e.g., an analeptic agent such as *d*-amphetamine, as found in the commercial ADHD product Adderol®). It has now been discovered that co-administering methylphenidate, and particularly *d-threo*
20 methylphenidate, with a second CNS stimulant, particularly an analeptic agent such as *d*-amphetamine, gives rise to a therapeutically effective pharmaceutical formulation useful in treating individuals who do not respond, or respond inadequately, to methylphenidate therapy or to the second CNS stimulant, when administered as individual active agents. It has also been found that the aforementioned combination of active agents can provide an increased therapeutic benefit to patients who do respond to methylphenidate therapy or to the second
25 CNS stimulant, e.g., to an analeptic agent such as *d*-amphetamine.

Accordingly, the present invention provides novel pharmaceutical dosage forms for the administration of *d-threo* methylphenidate along with at least one additional active agent comprising a second CNS stimulant. The novel dosage forms provide for pulsatile drug release, thereby maximizing efficacy (i.e., the loss of clinical efficacy over time), reducing the
30 potential for abuse or noncompliance. The dosage forms also provide for therapeutic efficacy in individuals who do not respond, or respond inadequately, to methylphenidate or to the

second CNS stimulant when these agents are administered alone, and provide enhanced therapeutic efficacy in individuals who are responsive to methylphenidate and other CNS stimulants such as *d*-amphetamine. No art of which applicants are aware describes drug delivery systems as now provided herein.

- 5 To the best of applicants' knowledge, the pharmaceutical dosage forms of the invention are previously unknown and completely unsuggested by the art.

DISCLOSURE OF THE INVENTION

- 10 Accordingly, it is a primary object of the invention to address the above-mentioned need in the art by providing a pharmaceutical dosage form for pulsatile delivery of *d-threo* methylphenidate, wherein the dosage form contains a second CNS stimulant as an additional active agent.

- 15 It is another object of the invention to provide such a dosage form comprising at least two individual drug-containing dosage units, each of which has a different drug release profile.

 It is another object of the invention to provide such a dosage form wherein the dosage units are housed in a closed capsule.

 It is still another object of the invention to provide such a dosage form wherein the dosage units are compressed tablets.

- 20 It is yet another object of the invention to provide such a dosage form wherein the dosage units are drug-containing particles or beads.

 It is a further object of the invention to provide such a dosage form comprised of a single tablet of which the drug-containing dosage units represent integral and discrete segments.

- 25 It is still a further object of the invention to provide such a dosage form wherein the second CNS stimulant is an analeptic agent or psychostimulant.

 It is an additional object of the invention to provide methods for administering methylphenidate using the novel dosage forms.

- 30 Additional objects, advantages and novel features of the invention will be set forth in part in the description which follows, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the invention.

MODES FOR CARRYING OUT THE INVENTION

DEFINITIONS AND NOMENCLATURE:

Before the present formulations and methods of use are disclosed and described, it is to be understood that unless otherwise indicated this invention is not limited to specific
5 pharmacologically active agents, specific pharmaceutical carriers, or to particular administration regimens, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

It must be noted that, as used in the specification and the appended claims, the
10 singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an active agent" includes mixtures of active agents, "a second agent" includes more than one "second" agent, reference to "a pharmaceutical carrier" includes combinations of two or more carriers, and the like.

In this specification and in the claims which follow, reference will be made to a
15 number of terms which shall be defined to have the following meanings:

"Optional" or "optionally" means that the subsequently described circumstance may or may not occur, so that the description includes instances where the circumstance occurs and instances where it does not.

The terms "active agent," "drug" and "pharmacologically active agent" are used
20 interchangeably herein to refer to a chemical material or compound which, when administered to an organism (human or animal, generally human) induces a desired pharmacologic effect. In the context of the present invention, the terms refer to a compound that is capable of being delivered orally.

By the terms "effective amount" or "pharmaceutically effective amount" of an agent
25 as provided herein are meant a nontoxic but sufficient amount of the agent to provide the desired therapeutic effect. The exact amount required will vary from subject to subject, depending on age, general condition of the subject, the severity of the condition being treated, and the particular active agent administered, and the like. Thus, it is not possible to specify an exact "effective amount." However, an appropriate "effective" amount in any individual
30 case may be determined by one of ordinary skill in the art using routine experimentation.

By "pharmaceutically acceptable" carrier is meant a carrier comprised of a material that is not biologically or otherwise undesirable, i.e., the material may be administered to an individual along with the selected active agent without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained. The term "carrier" is used generically herein to refer to any components present in the pharmaceutical formulations other than the active agent or agents, and thus includes diluents, binders, lubricants, disintegrants, fillers, coloring agents, wetting or emulsifying agents, pH buffering agents, preservatives, and the like.

Similarly, a "pharmaceutically acceptable" salt or a "pharmaceutically acceptable" ester of a compound as provided herein is a salt or ester which is not biologically or otherwise undesirable.

In the chemical structures drawn herein, the use of bold and dashed lines to denote particular conformation of substituents follows IUPAC convention. The symbols " α " and " β " indicate the specific stereochemical configuration of a substituent at an asymmetric carbon atom in a chemical structure as drawn. Thus " α ," denoted by a broken line, indicates that the group in question is below the general plane of the molecule as drawn, and " β ," denoted by a bold line, indicates that the group at the position in question is above the general plane of the molecule as drawn.

"PULSATILE RELEASE" DOSAGE FORMS:

In a first embodiment, the invention features pharmaceutical dosage forms that provide for pulsatile delivery of *d-threo*-methylphenidate, with a second CNS stimulant co-administered with the *d-threo*-methylphenidate in at least one of the drug release "pulses." By "pulsatile" is meant that a plurality of drug doses are released at spaced apart time intervals. Generally, upon ingestion of the dosage form, release of the initial dose is substantially immediate, i.e., the first drug release "pulse" occurs within 1-2 hours of ingestion. This initial pulse is followed by a first time interval during which substantially no drug is released from the dosage form, after which a second dose is then released. Typically, the second dose is released on the order of 3-5 hours following ingestion of the dosage form. Preferably, release of the second dose is followed by a second non-release interval, which is again followed by a "pulse" of drug release. Ideally, release of a third dose occurs on the

order of 7-9 hours following ingestion. In a preferred embodiment herein, either two or three release pulses are provided. However, the invention is also intended to encompass dosage forms that provide more than three pulses, with non-release intervals therebetween of approximately 2-6 hours, preferably 3-5 hours.

5 The aforementioned pulsatile release profile is achieved with dosage forms that, in one embodiment, are closed and preferably sealed capsules housing two or more drug-containing "dosage units." In a preferred embodiment, each dosage unit comprises a compressed or molded tablet, wherein each of the tablets within the capsule provides a different drug release profile. That is, for an exemplary dosage form, a first tablet releases
10 drug substantially immediately following ingestion of the dosage form, while a second tablet in the capsule releases drug approximately 3-5 hours following ingestion, and an optional third tablet provides drug release after approximately 7-9 hours. While the dosage form will not generally include more than three tablets, dosage forms housing four or more tablets are within the scope of the present invention.

15 In an alternative embodiment, each dosage unit comprises a drug-containing particle or bead (drug-containing "beads" refer to drug-coated inert supports, e.g., lactose beads coated with drug). A first group of these particles or beads releases drug substantially immediately following ingestion of the dosage form, a second group releases drug
20 approximately 3-5 hours following ingestion, and an optional third group provides drug release after approximately 7-9 hours.

 In a further alternative embodiment, the individual dosage units are compacted in a single tablet, and represent integral but discrete segments thereof (e.g., layers). For example, drug-containing particles or drug-containing beads can be compressed together into a single tablet using conventional tableting means.

25 As will be appreciated by those skilled in the art and as described in the pertinent texts and literature, a number of methods are available for preparing drug-containing tablets or other dosage units which provide a variety of drug release profiles. Such methods include coating a drug or drug-containing composition, increasing the drug's particle size, placing the drug within a matrix, and forming complexes of the drug with a suitable complexing agent.

30 The delayed release dosage units in the present capsules can be prepared, for example, by coating a drug or a drug-containing composition with a selected membrane coating

material, typically although not necessarily a polymeric material. When a coating is used to provide delayed release dosage units, particularly preferred coating materials comprise bioerodible, gradually hydrolyzable and/or gradually water-soluble polymers. The "coating weight," or relative amount of coating material per dosage unit, generally dictates the time interval between ingestion and drug release.

Suitable membrane coating materials for effecting delayed release include, but are not limited to: cellulosic polymers such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, ethyl cellulose, cellulose acetate, cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropylmethyl cellulose phthalate, cellulose ester-ether phthalate, hydroxypropylcellulose phthalate, alkali salts of cellulose acetate phthalate, alkaline earth salts of cellulose acetate phthalate, hydroxypropylmethyl cellulose hexahydrophthalate, cellulose acetate hexahydrophthalate, and carboxymethylcellulose sodium; acrylic acid polymers and copolymers preferably formed from acrylic acid, methacrylic acid, acrylic acid alkyl esters, methacrylic acid alkyl esters, and the like, e.g. copolymers of acrylic acid, methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate, with a terpolymer of ethyl acrylate, methyl methacrylate and trimethylammonioethyl methacrylate chloride (sold under the tradename Eudragit RS) particularly preferred; vinyl polymers and copolymers such as polyvinyl pyrrolidone, polyvinyl acetate, polyvinylacetate phthalate, vinylacetate crotonic acid copolymer, and ethylene-vinyl acetate copolymers; and shellac, ammoniated shellac, shellac-acetyl alcohol, and shellac *n*-butyl stearate.

In some cases, it may be desirable for the third tablet or bead or particle fraction to provide for release of the active agent in the colon, in which case polymeric or other materials are used that enable drug release within the colon. These may be selected from the aforementioned list, or other materials may be used as will be known to those skilled in the art of pharmaceutical formulation and drug delivery. For example, hydrocolloid gums may be effective to provide for colonic delivery, e.g., guar gum, locust gum, bena gum, gum tragacanth, and karaya gum (see, e.g., U.S. Patent No. 5,656,294 to Friend). Other materials suitable for effecting colonic drug delivery include polysaccharides, mucopolysaccharides, and related compounds, e.g., pectin, arabinogalactose, chitosan, chondroitin sulfate, dextran, galactomannan, and xylan.

Combinations of different coating materials may also be used to coat a single dosage unit.

To bring about the desired pulsatile release profile for a dosage form comprised of encapsulated tablets, the first tablet is provided with little or no coating material, the second
5 tablet is provided with some degree of coating material, the coating weight of a third tablet is still higher, and so on. Analogously, for encapsulated dosage forms in which the drug-containing dosage units are beads or particles, a first fraction of beads or particles is provided with little or no coating material, a second fraction is provided with some degree of coating material, the coating weight of a third fraction is still higher, etc. For example, when the
10 dosage form contains three tablets (or, analogously, three groups of drug-containing particles or beads), the first tablet, which releases drug substantially immediately, may have a total coating weight of less than about 10%, preferably less than about 8%, the second tablet may have a total coating weight in the range of approximately 10% to 30%, preferably 15% to 25%, and the third tablet, if present, may have a total coating weight in the range of
15 approximately 15% to 65%, preferably 20% to 65%. The preferred coating weights for particular coating materials may be readily determined by those skilled in the art by evaluating individual release profiles for dosage units prepared with different quantities of various coating materials.

Alternatively, the delayed release dosage units, i.e., tablets or drug-containing
20 particles, may be formulated by dispersing the drug within a matrix of a suitable material such as an insoluble plastic, a hydrophilic polymer, or a fatty compound. The insoluble plastic matrices may be comprised of, for example, polyvinyl chloride or polyethylene. Hydrophilic polymers useful for providing a matrix for a delayed release dosage unit include, but are not limited to, those described above as suitable coating materials. Fatty compounds for use as a
25 matrix material include, but are not limited to, waxes generally (e.g., carnauba wax) and glyceryl tristearate. Once the active ingredient is mixed with the matrix material, the mixture can be compressed into tablets or processed into individual drug-containing particles.

The individual dosage units may be provided with colored coatings, with a single color used to identify a tablet or bead or particle fraction having a corresponding delayed
30 release profile. That is, for example, a blue coating may be used for the immediate release tablet or bead or particle fraction, a red coating may be used for the "medium" release tablet

or bead or particle fraction, and the like. In this way, errors during manufacture can be easily avoided. The color is introduced by incorporating a pharmaceutically acceptable colorant into the coating during coating preparation. The colorant may be either natural or synthetic. Natural colorants include pigments such as chlorophyll, anattoes, beta-carotene, alizarin, indigo, rutin, hesperidin, quercetin, carminic acid, and 6,6'-dibromoindigo. Synthetic colorants are dyes, including both acidic dyes and basic dyes, such as nitroso dyes, nitro dyes, azo dyes, oxazines, thiazines, pyrazolones, xanthenes, indigoids, anthraquinones, acridines, rosanilines, phthaleins, quinolines. e.g., a dye or pigment, during preparation of the coating solution.

For encapsulated tablets, the weight of each individual tablet in the capsule is typically in the range of about 10 mg to 150 mg, preferably in the range of about 25 mg to about 100 mg, and most preferably is in the range of about 40 mg to 80 mg. The individual tablets are prepared using conventional means. A preferred method for forming tablets herein is by direct compression of a powdered, crystalline or granular drug-containing composition, alone or in combination with diluents, binders, lubricants, disintegrants, colorants or the like. As an alternative to direct compression, compressed tablets can be prepared using wet-granulation or dry-granulation processes. Tablets may also be molded rather than compressed, starting with a moist material containing a suitable water-soluble lubricant. Preferred tablets herein are manufactured using compression rather than molding, however. Drug-containing particles or beads are also prepared using conventional means, typically from a fluid dispersion.

Conventional coating procedures and equipment may then be used to coat the dosage units, i.e., the drug-containing tablets, beads or particles. For example, a delayed release coating composition may be applied using a coating pan, an airless spray technique, fluidized bed coating equipment, or the like. For detailed information concerning materials, equipment and processes for preparing tablets, beads and delayed release dosage forms, reference may be had to *Pharmaceutical Dosage Forms: Tablets*, eds. Lieberman et al. (New York: Marcel Dekker, Inc., 1989), and to Ansel et al., *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 6th Ed. (Media, PA: Williams & Wilkins, 1995).

Optional components present in the individual drug-containing dosage units include, but are not limited to, diluents, binders, lubricants, disintegrants, stabilizers, surfactants,

coloring agents, and the like. Diluents, also termed "fillers," are typically necessary to increase the bulk of a tablet so that a practical size is provided for compression. Suitable diluents include, for example, dicalcium phosphate dihydrate, calcium sulfate, lactose, cellulose, kaolin, mannitol, sodium chloride, dry starch, hydrolyzed starches, silicon dioxide, titanium oxide, alumina, talc, microcrystalline cellulose, and powdered sugar. Binders are used to impart cohesive qualities to a tablet formulation, and thus ensure that a tablet remains intact after compression. Suitable binder materials include, but are not limited to, starch (including corn starch and pregelatinized starch), gelatin, sugars (including sucrose, glucose, dextrose, lactose and sorbitol), polyethylene glycol, waxes, natural and synthetic gums, e.g., acacia, tragacanth, sodium alginate, polyvinylpyrrolidone, celluloses, and Veegum, and synthetic polymers such as polymethacrylates and polyvinylpyrrolidone. Lubricants are used to facilitate tablet manufacture; examples of suitable lubricants include, for example, magnesium stearate, calcium stearate, stearic acid, glyceryl behenate, and polyethylene glycol, and are preferably present at no more than approximately 1 wt.% relative to tablet weight.

Disintegrants are used to facilitate tablet disintegration or "breakup" after administration, and are generally starches, clays, celluloses, algin, gums or crosslinked polymers. Stabilizers are used to inhibit or retard drug decomposition reactions which include, by way of example, oxidative reactions. Surfactants may be anionic, cationic, amphoteric or nonionic surface active agents, with anionic surfactants preferred. Suitable anionic surfactants include, but are not limited to, those containing carboxylate, sulfonate and sulfate ions, associated with cations such as sodium, potassium and ammonium ions. Particularly preferred surfactants include, but are not limited to: long alkyl chain sulfonates and alkyl aryl sulfonates such as sodium dodecylbenzene sulfonate; dialkyl sodium sulfosuccinates, such as sodium bis-(2-ethylhexyl)-sulfosuccinate; and alkyl sulfates such as sodium lauryl sulfate. If desired, the tablets may also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, preservatives, and the like.

As noted earlier herein, the individual drug tablets, beads or particles are contained within a closed capsule. The capsule material may be either hard or soft, and as will be appreciated by those skilled in the art of pharmaceutical science, typically comprises a tasteless, easily administered and water soluble compound such as gelatin, starch or cellulose. A preferred capsule material is gelatin. The capsules are preferably sealed, such as with

gelatin bands or the like. See, for example, *Remington: The Science and Practice of Pharmacy*, Nineteenth Edition (Easton, PA: Mack Publishing Co., 1995), which describes materials and methods for preparing encapsulated pharmaceuticals designed to dissolve shortly after ingestion.

5 The novel dosage forms provided herein are used to administer *d-threo*-methylphenidate in a pulsatile release manner. As noted earlier herein, the drug is administered along with a second CNS stimulant. The second CNS stimulant, which may potentiate the effect of the *d-threo*-methylphenidate, or vice versa, is generally an analeptic agent or psychostimulant.

10 Preferred CNS stimulants include, but are not limited to: amphetamine (racemic), *d*-amphetamine, amphetamine and *d*-amphetamine phosphate, amphetamine and *d*-amphetamine sulfate, amphetamine and *d*-amphetamine hydrochloride, amphetamine and *d*-amphetamine saccharate, and amphetamine and *d*-amphetamine aspartate, amphetaminil, bemegride, benzphetamine, benzphetamine hydrochloride, brucine, chlorphentermine,
15 clofenciclan, clortermine, deanol acetamidobenzoate, demanyl phosphate, dexoxadrol, diethpropion, doxapram hydrochloride, N-ethylamphetamine, ethamivan, etifelmin, etryptamine, fencamfamine, fenethylline, fenosolone, fenfluramine, flurothyl, hexacyclonate sodium, homocamfin, mazindol, megexamide, methamphetamine, nicotinic agonists, nikethamide, pemoline, pentylenetetrazole, phenidimetrazine, phendimetrazine tartrate,
20 phenmetrazine, phenmetrazine hydrochloride, phentermine, picrotoxin, pipradrol, pipradrol hydrochloride, prolintane, pyrovalerone, racephedrine, racephedrine hydrochloride, and tetrahydrobenzothienopyridines. Pemoline, amphetamine, *d*-amphetamine and salts thereof are particularly preferred additional active agents.

 The additional active agent or agents may be combined with the *d-threo*-
25 methylphenidate in a single tablet or bead or particle fraction within the capsule, or one or more tablets or bead fractions within the capsule may comprise the additional active agent without any methylphenidate. In the former case, the various active agents may be present as an admixture in a single dosage unit (e.g., a tablet), or the agents may be physically segregated as in a bilayer tablet, a tablet having two or more active agent-containing coatings,
30 or the like. Generally, the additional CNS stimulant such as *d*-amphetamine will be included in the first, immediate release tablet or bead or particle fraction, will optionally be present in

the second tablet or bead or particle fraction (and if present, at a lower dose than in the first tablet or bead or particle fraction), and will not be included in the third tablet or bead or particle fraction. Ideally, the relative amounts of the active agents in the dosage forms of the invention are as follows:

5

First tablet or bead (or particle) fraction: Contains a dose "X" of *d-threo*-methylphenidate and a dose "Y" of a second CNS stimulant (e.g., an analeptic agent such as *d*-amphetamine), wherein the molar ratio of X:Y is in the range of approximately 2:1 to 1:2. The dose "X" represents approximately half of that which would be appropriate for dosage of *d,l-threo*-methylphenidate, and is typically in the range of approximately 1 mg to 20 mg, preferably 1 mg to 10 mg. When the second CNS stimulant is *d*-amphetamine, "Y" is typically in the range of approximately 1 mg to 20 mg, preferably 1 mg to 10 mg.

10

Second tablet or bead (or particle) fraction: Contains a dose of *d-threo*-methylphenidate in the range of approximately 0.5X to 2X, preferably 1X to 2X, and a dose of the second CNS stimulant in the range of zero to 0.5Y.

15

Third tablet or bead (or particle) fraction, if present: Contains a dose of *d-threo*-methylphenidate in the range of approximately 0.25X to 1X, optimally about 0.5X to 1X, and contains none of the second CNS stimulant.

Thus, the second CNS stimulant, present in the first pulse, is optionally included in the second pulse, and if present, is at a lower dose (up to half) of the amount in the first pulse. The third tablet or bead or particle fraction should contain a lower dose of *d-threo*-methylphenidate than either the first or second pulses, and should not contain any of the second CNS stimulant. In this way, the potential for sleep disruption is minimized.

20

Salts of the active agents used in conjunction with the present dosage forms may be obtained commercially or can be prepared using standard procedures known to those skilled in the art of synthetic organic chemistry and described, for example, by J. March, *Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 4th Ed. (New York: Wiley-Interscience, 1992). Suitable acids for preparing acid addition salts may be weak acids, medium acids, or strong acids, and include both organic acids, e.g., acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, aspartic acid, saccharic acid, tartaric acid, citric acid, benzoic acid,

30

cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like, as well as inorganic acids, e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Preparation of basic salts of acid moieties which may be present (e.g., carboxylic acid groups) are prepared using a pharmaceutically acceptable base such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, magnesium hydroxide, trimethylamine, or the like. Preparation of esters involves functionalization of hydroxyl and/or carboxyl groups which may be present. These esters are typically acyl-substituted derivatives of free alcohol groups, i.e., moieties which are derived from carboxylic acids of the formula RCOOH where R is alkyl, and preferably is lower alkyl. Pharmaceutically acceptable esters may be prepared using methods known to those skilled in the art and/or described in the pertinent literature. Amides, prodrugs, and other analogs and derivatives can be readily prepared as well, using conventional means.

15 UTILITY:

The novel drug dosage forms are to be administered orally to a mammalian individual and can be used to administer *d-threo*-methylphenidate to treat or prevent a variety of disorders, conditions and diseases. In accordance with the present invention, administration of *d-threo*-methylphenidate along with the second CNS stimulant may be carried out in order to treat any disorder, condition or disease for which methylphenidate is generally indicated. Such disorders, conditions and diseases include, for example, ADD, ADHD, narcolepsy, and acute depression; methylphenidate may also be used in the treatment of individuals suffering from cognitive decline associated with AIDS or AIDS-related conditions, and for mood elevation in terminally ill patients suffering from a disease such as cancer.

For administration of *d-threo*-methylphenidate, the typical daily dose is in the range of approximately 2.5 mg to 50 mg, preferably 5 mg to 60 mg, although the exact dosage regimen will depend on a number of factors, including age, the general condition of the patient, the particular condition or disorder being treated, the severity of the patient's condition or disorder, and the like.

It is to be understood that while the invention has been described in conjunction with the preferred specific embodiments thereof, that the description above as well as the examples which follow are intended to illustrate and not limit the scope of the invention. Other aspects, advantages and modifications within the scope of the invention will be apparent to those skilled in the art to which the invention pertains.

EXPERIMENTAL:

The practice of the present invention will employ, unless otherwise indicated, conventional techniques of pharmaceutical formulation, medicinal chemistry, biological testing, and the like, which are within the skill of the art. Such techniques are explained fully in the literature. Preparation of various types of pharmaceutical formulations are described, for example, in Lieberman et al., cited supra; synthesis of chiral drugs is described, *inter alia*, in Wilson and Gisvold, *Textbook of Organic, Medicinal and Pharmaceutical Chemistry* (Lippincott-Raven Publishers, 1991); and Gibaldi and Perrier, *Pharmacokinetics* (Marcel Dekker, 1982), provides a description of the biological testing procedures useful to evaluate compounds such as those described and claimed herein.

In the following examples, efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental error and deviation should be accounted for. Unless indicated otherwise, temperature is in degrees C and pressure is at or near atmospheric. All reagents were obtained commercially unless otherwise indicated.

EXAMPLE 1

PULSATILE DELIVERY SYSTEM FOR ORAL ADMINISTRATION OF ***d-threo* METHYLPHENIDATE AND *d*-AMPHETAMINE**

A pulsatile release dosage form for administration of *d-threo*-methylphenidate and *d*-amphetamine is prepared by (1) formulating three individual compressed tablets, each having a different release profile, followed by (2) encapsulating the three tablets into a gelatin

capsule and then closing and sealing the capsule. The components of the three tablets are as follows.

TABLET 1 (IMMEDIATE RELEASE):

Component	Function	Amount per tablet
<i>d-threo</i> -methylphenidate	Active agent	2.5 mg
<i>d</i> -amphetamine	Active agent	2.5 mg
Dicalcium phosphate dihydrate	Diluent	26.6 mg
Microcrystalline cellulose	Diluent	26.6 mg
Sodium starch glycolate	Disintegrant	1.2 mg
Magnesium Stearate	Lubricant	0.6 mg

TABLET 2 (RELEASE DELAYED 3-5 HOURS FOLLOWING ADMINISTRATION):

Component	Function	Amount per tablet
<i>d-threo</i> methylphenidate	Active agent	2.5 mg
<i>d</i> -amphetamine	Active agent	1.25 mg
Dicalcium phosphate dihydrate	Diluent	26.6 mg
Microcrystalline cellulose	Diluent	26.6 mg
Sodium starch glycolate	Disintegrant	1.2 mg
Magnesium Stearate	Lubricant	0.6 mg
Eudragit RS30D	Delayed release coating material	4.76 mg
Talc	Coating component	3.3 mg
Triethyl citrate	Coating component	0.95 mg

TABLET 3 (RELEASE DELAYED 7-9 HOURS FOLLOWING ADMINISTRATION):

Component	Function	Amount per tablet
<i>d-threo</i> methylphenidate	Active agent	2.5 mg
Dicalcium phosphate dihydrate	Diluent	26.6 mg
Microcrystalline cellulose	Diluent	26.6 mg
Sodium starch glycolate	Disintegrant	1.2 mg
Magnesium Stearate	Lubricant	0.6 mg
Eudragit RS30D	Delayed release coating material	6.34 mg
Talc	Coating component	4.4 mg
Triethyl citrate	Coating component	1.27 mg

The tablets are prepared by wet granulation of the individual drug particles and other core components as may be done using a fluid-bed granulator, or are prepared by direct compression of the admixture of components. Tablet 1 is an immediate release dosage form, releasing the active agents within 1-2 hours following administration. Tablets 2 and 3 are coated with the delayed release coating material as may be carried out using conventional coating techniques such as spray-coating or the like. As will be appreciated by those skilled in the art, the specific components listed in the above tables may be replaced with other functionally equivalent components, e.g., diluents, binders, lubricants, fillers, coatings, and the like.

Oral administration of the capsule to a patient will result in a release profile having three pulses, with initial release of the *d-threo*-methylphenidate and *d*-amphetamine from the first tablet being substantially immediate, release of the *d-threo*-methylphenidate and *d*-amphetamine from the second tablet occurring 3-5 hours following administration, and release of the *d-threo*-methylphenidate from the third tablet occurring 7-9 hours following administration. Because Tablet 3 contains a lower dosage of *d-threo*-methylphenidate than Tablets 1 or 2, and no *d*-amphetamine, the likelihood of sleep disruption is substantially reduced.

EXAMPLE 2

The method of Example 1 is repeated, except that drug-containing beads are used in place of tablets. A first fraction of beads may be prepared by coating an inert support material such as lactose with the drug which provides the first (immediate release) pulse. A second
5 fraction of beads is prepared by coating immediate release beads with an amount of enteric coating material sufficient to provide a drug release-free period of 3-5 hours. A third fraction of beads is prepared by coating immediate release beads having half the methylphenidate dose of the first fraction of beads with a greater amount of enteric coating material, sufficient to provide a drug release-free period of 7-9 hours. The three groups of beads may be
10 encapsulated as in Example 1, or compressed, in the presence of a cushioning agent, into a single pulsatile release tablet.

Alternatively, three groups of drug particles may be provided and coated as above, in lieu of the drug-coated lactose beads.

CLAIMS:

1. A pulsatile release dosage form for oral administration of methylphenidate, comprising:

5 (a) a first dosage unit comprising a first *d-threo*-methylphenidate dose X and a first dose Y of a CNS stimulant other than *d-threo*-methylphenidate that are released substantially immediately following oral administration of the dosage form to a patient;

(b) a second dosage unit comprising a second *d-threo*-methylphenidate dose and optionally a second dose of the CNS stimulant, and a means for delaying release of the second
10 doses until approximately 3 to 5 hours following administration of the dosage form to a patient; and optionally

(c) a third dosage unit comprising a third *d-threo*-methylphenidate dose without the CNS stimulant, and a means for delaying release of the third dose until approximately 7 to 9 hours following oral administration of the dosage form to a patient.

15

2. The dosage form of claim 1, wherein X and Y have a molar ratio in the range of approximately 1:2 to 2:1.

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3. The dosage form of claim 2, wherein X is in the range of approximately 1 mg to 20 mg.

4. The dosage form of claim 3, wherein X is in the range of approximately 1 mg to 10 mg.

25

5. The dosage form of claim 3, wherein the second dose of *d-threo*-methylphenidate is approximately 0.5X to 2X, and the second dose of the CNS stimulant is in the range of zero to approximately 0.5Y.

30

6. The dosage form of claim 1, wherein the third dosage unit is present.

7. The dosage form of claim 5, wherein the third dosage unit is present.

8. The dosage form of claim 7, wherein the third dose of *d-threo*-methylphenidate is approximately 0.25X to 1X.

5 9. The dosage form of claim 6, wherein the first, second and third dosage units are housed in a closed capsule.

10 10. The dosage form of claim 6, wherein the first, second and third dosage units represent integral and discrete segments of a single tablet.

11. The dosage form of claim 9, wherein each dosage unit comprises a compressed tablet.

12. The dosage form of claim 9, wherein each dosage unit comprises a plurality of drug-containing beads.

15 13. The dosage form of claim 9, wherein each dosage unit comprises a plurality of drug-containing particles.

20 14. The dosage form of claim 6, wherein the third dosage unit releases the third *d-threo*-methylphenidate dose in the colon.

15. The dosage form of claim 1, wherein the CNS stimulant is an analeptic agent.

25 16. The dosage form of claim 1, wherein the CNS stimulant is selected from the group consisting of amphetamine, *d*-amphetamine, amphetaminil, bemegride, benzphetamine, benzphetamine, brucine, chlorphentermine, clofenciclan, clortermine, deanol acetamidobenzoate, demanyl, dexoadrol, diethpropion, doxapram, N-ethylamphetamine, ethamivan, etifelmin, etryptamine, fencamfamine, fenethylline, fenosolone, fenfluramine, flurothyl, hexacyclonate, homocamfin, mazindol, megexamide, methamphetamine, nicotinic
30 agonists, nikethamide, pemoline, pentylenetetrazole, phenidimetrazine, phendimetrazine, phenmetrazine, phenmetrazine, phentermine, picrotoxin, pipradrol, prolintane, pyrovalerone,

racephedrine, tetrahydrobenzothienopyridines, and pharmacologically acceptable salts thereof.

5 17. The dosage form of claim 16, wherein the CNS stimulant is selected from the group consisting of amphetamine, *d*-amphetamine, and pharmacologically acceptable salts thereof.

10 18. The dosage form of claim 17, wherein the CNS stimulant is selected from the group consisting of amphetamine, *d*-amphetamine, amphetamine phosphate, *d*-amphetamine phosphate, amphetamine sulfate, *d*-amphetamine sulfate, amphetamine hydrochloride, *d*-amphetamine hydrochloride, amphetamine saccharate, *d*-amphetamine saccharate, amphetamine aspartate, *d*-amphetamine aspartate, and combinations thereof.

15 19. The dosage form of claim 16, wherein the CNS stimulant is pemoline.

20. The dosage form of claim 1, wherein the means for delaying release comprises a coating of a delayed release membrane material.

20 21. The dosage form of claim 20, wherein the delayed release membrane material is comprised of a bioerodible, hydrolyzable and/or gradually water-soluble polymer.

22. The dosage form of claim 21, wherein the delayed release membrane material is an acrylic resin.

25 23. The dosage form of claim 22, wherein the delayed release membrane material is a copolymer of acrylic acid, methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate, ethyl methacrylate, and/or derivatives thereof.

30 24. The dosage form of claim 22, wherein the delayed release membrane material is a terpolymer of ethyl acrylate, methyl methacrylate and trimethylammonioethyl methacrylate chloride.

25. The dosage form of claim 1, wherein at least one of the first, second and third dosage units further comprises a diluent.

5 26. The dosage form of claim 25, wherein the diluent is selected from the group consisting of dicalcium phosphate dihydrate, calcium sulfate, lactose, cellulose, kaolin, mannitol, dry starch, hydrolyzed starches, silicon dioxide, titanium oxide, alumina, talc, microcrystalline cellulose, powdered sugar, and mixtures thereof.

10 27. The dosage form of claim of claim 1, wherein at least one of the first, second and third dosage units further comprises a lubricant.

15 28. The dosage form of claim 27, wherein the lubricant is selected from the group consisting of magnesium stearate, calcium stearate, stearic acid, glyceryl behenate, polyethylene glycol, and mixtures thereof.

29. The dosage form of claim 28, wherein the lubricant is magnesium stearate.

20 30. The dosage form of claim 1, wherein at least one of the first, second and third dosage units further comprises a disintegrant.

31. The dosage form of claim 30, wherein the disintegrant is sodium starch glycolate.

32. The dosage form of claim 1, wherein each dosage unit has a different color.

25 33. A method for treating an individual suffering from ADD, comprising administering to the individual, once daily, the dosage form of claim 1.

30 34. A method for treating an individual suffering from ADHD, comprising administering to the individual, once daily, the dosage form of claim 1.

35. A method for treating an individual suffering from narcolepsy, comprising administering to the individual, once daily, the dosage form of claim 1.

5 36. A method for treating an individual suffering from acute depression, comprising administering to the individual, once daily, the dosage form of claim 1.

10 37. A method for treating an individual suffering from cognitive decline associated with Acquired Immunodeficiency Syndrome ("AIDS") or AIDS-related conditions, comprising administering to the individual, once daily, the dosage form of claim 1.

38. A method for elevating the mood of a terminally ill patient, comprising administering to the patient, once daily, the dosage form of claim 1.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/09472

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 9/20, 9/58

US CL : 424/459, 462, 464, 468; 514/317

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/459, 462, 464, 468; 514/317

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,837,284 A (MEHTA et al) 17 November 1998 (17.11.98), see entire document.	1-14, 20-38 ----- 1-38
Y	US 4,957,494 A (WONG et al) 18 September 1990 (18.09.90), see entire document.	15-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y"	document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

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